Humidification of indoor air for preventing or reducing dryness symptoms or upper respiratory infections in educational settings and at the workplace

Byber, Katarzyna ; Flatz, Aline ; Norbäck, Dan ; Hitzke, Christine ; Imo, David ; Schwenkglenks, Matthias ; Puhan, Milo Alan ; Dressel, Holger ; Mütsch, Margot

Abstract: This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: To evaluate the effectiveness of interventions that increase indoor air humidity to prevent or reduce dryness symptoms of the eyes, the skin and the upper respiratory tract (URT) or URT infections at work and in educational settings. Background Following the progress of industrialisation, workplaces have increasingly moved from outdoor to indoor locations. This shift has changed the spectrum of conditions to which workers are exposed. This fact is not only relevant to the adult working population, but also to children and young adults, as they stay indoors for a significant part of the day throughout their education (Angelon-Gaetz 2014; Jaakkola 1991; Seppanen 2002). At most workplaces, indoor air is a predefined condition. Its components vary considerably among different occupational and educational settings. Emissions from indoor sources like building materials, furnishings, office equipment and human activities result in the release of dust as well as chemical and biological compounds. Following natural ventilation, outdoor factors, such as pollen and particulate matters, may also contribute to indoor air quality (Alsmo 2014). Indoor air climate results from a combination of four physical parameters: temperature, radiation temperature, air velocity and humidity. Humidity is defined as absolute humidity (water vapour content of the air) whilst relative humidity (RH) is the ratio of vapour pressure and saturation vapour pressure. RH, expressed as a percentage, increases relative to a decrease in temperature. A humidity level of 100% means that the air is completely saturated with water vapour. The influence of different humidity levels on pathogens, allergens and chemical factors is presented in Figure 1 (Alsmo 2014).

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Humidification of indoor air for preventing or reducing dryness symptoms or upper respiratory infections in educational settings and at the workplace (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Humidification of indoor air for preventing or reducing dryness symptoms or upper respiratory infections in educational settings and at the workplace

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ABSTRACT

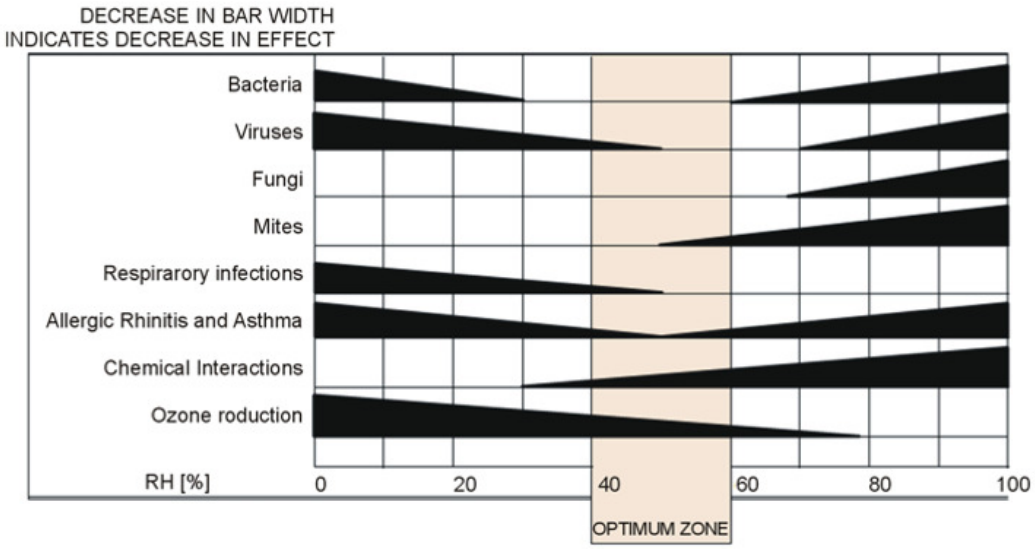
This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of interventions that increase indoor air humidity to prevent or reduce dryness symptoms of the eyes, the skin and the upper respiratory tract (URT) or URT infections at work and in educational settings.

BACKGROUND

Following the progress of industrialisation, workplaces have increasingly moved from outdoor to indoor locations. This shift has changed the spectrum of conditions to which workers are exposed. This fact is not only relevant to the adult working population, but also to children and young adults, as they stay indoors for a significant part of the day throughout their education (Angelon-Gaetz 2014; Jaakkola 1991; Seppanen 2002). At most workplaces, indoor air is a predefined condition. Its components vary considerably among different occupational and educational settings. Emissions from indoor sources like building materials, furnishings, office equipment and human activities result in the release of dust as well as chemical and biological compounds. Following natural ventilation, outdoor factors, such as pollen and particulate matters, may also contribute to indoor air quality (Alsmo 2014). Indoor air climate results from a combination of four physical parameters: temperature, radiation temperature, air velocity and humidity. Humidity is defined as absolute humidity (water vapour content of the air) whilst relative humidity (RH) is the ratio of vapour pressure and saturation vapour pressure. RH, expressed as a percentage, increases relative to a decrease in temperature. A humidity level of 100% means that the air is completely saturated with water vapour. The influence of different humidity levels on pathogens, allergens and chemical factors is presented in Figure 1 (Alsmo 2014).

Figure 1. Association of indoor relative humidity and exposure factors related to adverse health effects (Alsmo 2014)



Description of the condition

The context of indoor air humidity and health is not a new issue and the concept of dry air has been associated with poor air quality since the early 20th century (Watt 1910). Currently, there is no universal definition of dry air. It is in fact difficult to ascertain how and to what extent human beings perceive air humidity (von Hahn 2007), as we do not have any specific receptors to trace it directly. As the perception of dry air is strongly affected by climatic parameters (particularly temperature) and environmental factors (e.g. dust), even RH levels of 50% can be experienced as dry air under certain conditions (von Hahn 2007). Nevertheless, many recommend avoiding conditions below a lower limit of RH of 30% to 40%, as such conditions would commonly be perceived as uncomfortable (von Hahn 2007).

Naturally ventilated places have substantially lower levels of RH in winter than in summer. The colder it is outside and the better a building is naturally ventilated, the dryer indoor air becomes.

In cold seasons, building occupants increasingly complain about dryness symptoms of the eyes, throat and skin in close temporal relation to exposure to dry air at the workplace (von Hahn 2007). These symptoms lack specificity and therefore it is difficult to attribute them to clearly defined triggers. Furthermore, they can emerge through various pathways and, for instance, it may remain difficult to distinguish between symptoms due to immunological and inflammatory mechanisms. Some of these complaints are supposed to be directly associated with low levels of RH. However, the majority of them seem to be of multifactorial origin. In addition, they could also be the result of an indirect influence of RH due to interactions, for example with chronic illness. Individuals with certain pre-existing medical conditions and pre-disposed individuals appear to be more affected.

Ocular symptoms like burning, itching, and sensations of dryness and stinging are summarised as eye irritation (Wolkoff 2008). These complaints occur commonly at the workplace, especially in women (Wolkoff 2010). The prevalence of discomfort varies considerably and ranges from 5.5% to 33.7% across studies, depending on the investigated population and the diagnostic criteria (Lin 2003). Overall, office workers suffer more frequently from eye irritation than the general population (Wolkoff 2008). A low humidity level (5% to 30%) is an environmental risk factor that contributes to an increased prevalence of dry eyes in office environments (Wolkoff 2008). However, there is a wide range of individual and external risk factors associated with eye irritation in the office environment (Wolkoff 2008). Age, medication and hormonal changes represent personal risk factors for developing ocular symptoms (Wolkoff 2010). Exposure to ambient irritants such as formaldehyde and ozone can cause sensory irritation in the eyes by trigeminal stimulation (Wolkoff 2010). The impact of concomitant exposure to sensory irritants (e.g. volatile organic compounds (VOCs) and ozone) and dry air on the eye has been shown to be greater at a relative humidity level of 20% compared to 50% (Wolkoff 2005). Furthermore, irritated eye symptoms resulting from exposure to low humidity levels might be exacerbated by visual display unit work (Wolkoff 2007).

The mucous membrane of the airways poses a natural barrier protecting against irritants, microbes and unfavourable climatic con-

ditions. The interaction of ciliary activity and viscosity of mucosal fluid is crucial for its self-cleaning properties (Guggenbichler 2007). This mechanism is called mucociliary clearance and can be assessed using different methods. In the airways, the air is conditioned to 37°C and 100% relative humidity regardless of the ambient conditions (Pfluger 2013). However, despite this compensatory mechanism, exposure to dry air seems to induce dryness and irritation symptoms, as has been shown in several epidemiological studies (Ghaved 2005; Reinikainen 1991; Reinikainen 1992). Alongside age, air humidity and hydration status there are many other internal and external risk factors affecting mucous membrane function.

Among occupants of buildings, the baseline prevalence of nasal symptoms is often 20% (Bascom 1991). Building occupants exposed to chemical and microbiological VOCs can develop symptoms of mucosal irritation in the eyes and upper airways by trigeminal stimulation, even at levels below threshold values (Wolkoff 2013). Concomitant exposure to low humidity may lead to the instability of the mucous membrane and consequently to lowering the threshold of sensory irritation (Wolkoff 2013).

Occupants permanently exposed to low humidity commonly complain of dry, brittle and cracked skin (Pfluger 2013). A study by Rycroft 1980 described two outbreaks of dermatoses (pruritus, urticarial, erythema, oedema and scaling of the skin) relating to working environments with low RH (35%). Exposure to allergens and irritants in the workplace or at home may also lead to dryness or irritation symptoms of the skin and the development of dermatitis.

A review by Arundel 1986 suggests that RH can influence the incidence of respiratory infections. The incidence of absenteeism or respiratory infections was found to be lower among people working or living in environments with mid-range RH (50% to 70%) as opposed to low or high RH.

Experimental studies have shown that low humidity and low temperature promote the spread of influenza virus. Therefore, the winter time in temperate countries associated with exposure to cold air outdoors and its relationship with dry air indoors may explain the seasonality of influenza (Lowen 2014). Humidification of a building is often coupled with airflow and ventilation, which have been also found to influence the rate of transmission of respiratory tract viruses (Pica 2012).

Description of the intervention

The humidity level of indoor air can be increased by:

- central or building-level interventions that increase air humidity with air conditioning systems or whole house humidifiers,
- local or room-level interventions, such as separate air humidifiers that can be activated on demand, or
- other interventions, such as putting plants around the workplace or placing a container of water or wet clothes in proximity to a radiator or a heating system.

Technically, air humidity can be regulated with different types of humidifiers: steam humidifiers produce vapour by thermal evaporation; cold atomisers atomise water with a high-frequency ventilator; and the so-called ultrasound-atomisers create vapour by ultrasound waves (Fidler 1989). Re-circulated water can be used except for steam humidifiers. Overall, these different types of humidifiers use different techniques to increase air humidity and consequently, they may have different effects on health. When aiming to humidify indoor air, we also need to consider the effects of natural ventilation and seasonal variations as well as the influence on other factors of the indoor environment.

How the intervention might work

In order to achieve the recommended level of RH indoors and consequently to prevent dryness and irritation symptoms, workplaces and schools are being artificially humidified in some countries. There is, however, currently no clear evidence to advocate indoor air humidification.

The use of air humidifiers is often suggested to decrease the symptoms of dryness and irritation attributed to heating during winter, such as dry lips or eyes. This is a current opinion, but it has not been supported by all epidemiological and laboratory studies. Conflicting findings among studies can be explained by the use of different clinical scores to assess the outcomes, by diverse study populations being exposed to different ranges of RH, different exposure assessments and different study designs (Pfluger 2013). The variability of the study results may also be explained by the absence (in the majority of laboratory studies) or the presence (in studies conducted under real-life conditions) of a wide range of different indoor air factors affecting skin and mucous membranes. Some intervention studies have shown positive health effects of air humidification like an increase in the percentage of patients without dry and itchy skin (Hashiguchi 2008), alleviation of skin, pharyngeal, nasal dryness and congestion (Reinikainen 2003), significantly smaller dryness symptom scores for skin und mucosa (Reinikainen 1992) and a reduction in the number and frequency of skin und mucosa symptoms (Ghaved 2005).

Various studies, predominantly conducted under controlled laboratory conditions, have evaluated the subjectively experienced symptoms related to different humidity levels including objectively-assessed signs and measurements of physiological parameters. Exposure to dry air may lead to ocular dryness due to deficient tear secretion and altered tear film (Lang 2014). According to Pfluger 2013, independent studies have shown that exposure to dry air deteriorates the quality and stability of the tear film of the eyes. These changes consequently result in an increase of the eye blink frequency, which is one of the objective parameters measured in studies to assess the impact of dry air on ocular mucosa (Wolkoff 2008). Furthermore, there is a clear negative rela-

tionship between air humidity and evaporation (Pfluger 2013). A high evaporation rate reduces the quality of the tear film. These physiological changes concerning exposure to dry air may lead to ocular dryness symptoms which can be alleviated by an increase of the humidity level. Epidemiological and clinical studies suggest that 40% RH is a favourable condition for the precorneal tear film (Wolkoff 2008). Some studies have shown a correlation between increasing RH and more stable pre-corneal tear film measured by break-up time (Brasche 2005; Norbäck 2006; Wolkoff 2006). In a study conducted by Wyon 2006, the blink frequency was significantly lower at 35% than at 5% RH. There is experimental evidence that skin exposure to a low-humidity environment affects the superficial skin layers and decreases their water content (Egawa 2002). Increasing humidity levels can mitigate skin dryness. Wyon 2006 concludes that the water content of the skin measured with a corneometer was significantly higher at a humidity level of 35% than 15%.

Dehydration of the respiratory mucous membrane causes an increase in viscosity of the mucosal fluid and, as a consequence, ciliary clearance becomes less effective (Munkholm 2014). Elderly people, especially those living in nursing homes and staying in hospitals, seem to be more affected since they cannot regulate their water fluid balance by themselves. A relative humidity level below 25% leads to disadvantageous health effects in this group (Guggenbichler 2007).

When looking at experimental evidence, studies in young populations have found that low humidity did not influence the mucociliary clearance (Andersen 1972; Andersen 1974). However, a study investigating the young as well as the elderly population has shown impairment of mucous membrane functioning due to low RH levels of 10% amongst the elderly when compared to younger people (Sunwoo 2006).

According to the findings of his experimental and clinical investigations, Guggenbichler 2007 concluded that mucociliary clearance seems to be more efficient when the humidity level is at least 30%. A relative humidity of 45% is even better for the self-cleaning function of the airways. Water mist produced by several types of humidifiers reduces mucus viscosity (Arundel 1986).

Mucociliary clearance protects against bacterial and viral infection (Sahin-Yilmaz 2011). If exposure to dry air results in the impairment of mucociliary clearance and leads to irritation of the mucous membrane, as a consequence, the susceptibility to infections may be increased. This hypothesis is controversial, since only a number of studies with objective measurements have revealed pathophysiological damage of mucous membranes in the upper respiratory tract (URT) as a result of exposure to dry air. Alongside this direct effect of RH, the survival and transmission capacity of some respiratory viruses may be increased at a low level of absolute air humidity (Koep 2013; Makinen 2009; Shaman 2010). Overall, humidity and temperature affect host behavior (more time spent indoors during winter time), host defences (airways mucosal function is optimal at core temperature and high humidity) (Williams 1996) and the stability and infectivity of the viruses. Furthermore, humidity also affects the respiratory droplet size, which in turn influences the time infectious particles remain airborne and thus, can be inhaled.

Several, mostly older, epidemiological studies have evaluated the effect of humidity on the incidence of respiratory infections (Arundel 1986). The majority found a lower rate of respiratory infections in rooms with higher humidity compared to those with lower humidity. Most of these studies were conducted among preschool or school children, with only two studies conducted in adult workers. These latter two studies (Gubéran 1978; Serati 1969) found no significant differences in absenteeism due to respiratory tract infections between humidified and non-humidified offices. A study has shown that an increase in absolute humidity after humidification of the indoor environment resulted in a decreasing survival and transmission rate of the influenza virus (Koep 2013). At a humidity level of more than 40% the influenza virus infectivity decayed (Tellier 2006). The surface of lipid-containing viruses is supposedly inactivated at high atmospheric humidity levels (Shaman 2010). At high RH, large water-laden droplets settle on the ground which favours removal of infectious particles (Pica 2012).

Dryness symptoms of the eye, skin and URT, as well as fatigue and headache, are used to describe the term 'sick building syndrome' (SBS) (Joshi 2008; Norback 2009). These complaints seem to be directly linked to the time spent in a particular building. According to Burge 2004, air conditioned buildings have generally higher prevalence of symptomatic workers than those naturally ventilated. Although affected subjects perceive the sensation of dryness in enclosed spaces, it has been shown that they are not exposed to dry air (Burge 2004). It has been suggested that SBS may be associated with particular volatile organic compounds present in indoor air such as nitrogen dioxide, total volatile organic compounds and dust (Menzres 1996). It has also been postulated that exposure to allergens and irritants from humidifiers and conditioning systems could cause SBS (Burge 2004). However, the exact etiology of SBS remains unclear. Indeed, there are studies showing a positive effect of air humidification on SBS (Nordström 1994; Reinikainen 2001; Wyon 1992).

Humidifiers and air conditioning systems can be a source of microbial spread, such as bacteria, fungi and amoeba, which can be disseminated into the air and cause health problems, such as infections and allergic reactions. In particular, facilities that are not sufficiently cleaned and maintained (Suva 2012) can be colonised with micro-organisms. Furthermore, stagnant water in some humidifiers is linked to the so-called 'humidifier lung' (a type of hypersensitivity pneumonitis) and so-called 'humidifier fever' (a type of organic dust toxic syndrome).

In order to prevent pathogen growth, biocides are sometimes added to the water used for humidification. These substances may cause irritation or allergic reactions (Burge 2004).

As stated by the World Health Organization (WHO), RH of be-

tween 60% and 90% is favourable to the growth of mould, which is dependent on the growth medium, the mould species, the length of time in high relative air humidity and the measure of growth (WHO 2009).

Microbial growth as a result of high relative air humidity could also be a cause of SBS (Norback 2009).

Furthermore, air humidity has an impact on the emission rate of some indoor pollutants originating from building materials. This effect may increase or decrease the presence of these chemicals, such as formaldehyde (Haghighat 1998; Wolkoff 2007).

More recently, an increase in all-cause sick leave, which can be considered as a distal health outcome, has also been associated with the use of humidifiers in a manufactoring workplace (Milton 2000).

In summary, the effect of air humidity has been found to be dichotomised with a U-shaped association. Both low and high RH levels above 60% are associated with respiratory symptoms, highlighting that adverse health outcomes may occur at both extremes of the relative air humidity scale. Whereas the latter might result in dryness and irritation of the mucosa and the skin (Reinikainen 2003), the former might be related to infections associated with airborne microbial contamination (Wolkoff 2007).

See Figure 1 for an explanation of the association of indoor RH with exposure to adverse health-related factors by Alsmo 2014.

Why it is important to do this review

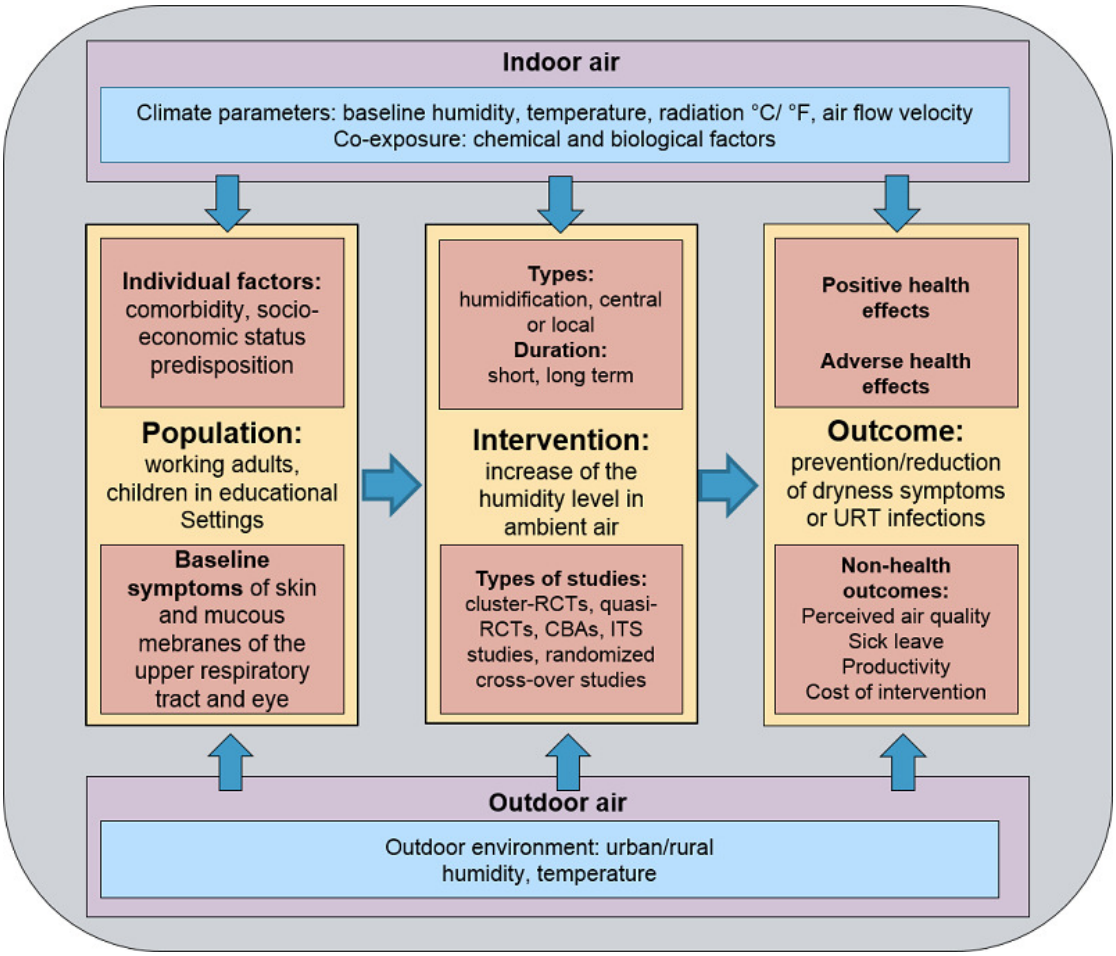
In Europe, recommendations concerning indoor relative air humidity differ between countries. In Switzerland, health authorities recommend at least 30% and a maximum of 65% RH to maintain a comfortable room climate (SECO 2011). However, there is no clear consensus on an optimal RH value, which may differ according to the working environment and the symptoms addressed. Concurrently, recommendations relating to the room temperature should be considered, since raising temperature leads to a decrease of RH. However, during heating periods, it is often not possible to achieve the recommended humidity range without active humidification. Further, acceptability of humidification may be of concern, because humidified air may be perceived to be of lower quality (Reinikainen 1997).

Here the question arises as to whether there is medical evidence behind the recommended RH range. In this context, Figure 1 is often shown, although its evidence base remains partially unknown. It seems questionable if it is generally possible to delineate a threshold at which physiological impairments occur, resulting in dryness and irritation symptoms of the skin and the mucous membranes and consequently, that may result in URT infections. In countries with temperate or cold climates, air humidification is needed to reach an RH of 30% or more during the heating season. The use of air humidifiers is associated with significant costs, notably of electricity. However, if low humidity is associated with adverse health outcomes, this itself would generate direct and indirect costs, such as healthcare visits, absenteeism and reduced productivity.

A number of literature reviews have assessed the influence of humidity on human health (Alsmo 2014; Arundel 1986; Green 1979; Guggenbichler 2007; Mendell 1993; Nagda 2001; Pfluger 2013; Pica 2012; von Hahn 2007; Wolkoff 2007; Wolkoff 2008) whilst, to date, no systematic review on this topic has been published. Furthermore, we are not aware of any previous Cochrane review that overlaps with this review. Consequently, there is an urgent need to compile the available evidence about health effects associated with air humidification amongst workers and in educational settings, respectively. Evidence has been accumulated over the past decades and it is important to integrate evidence originating from epidemiological (field) studies. One challenge may be to include older evidence, generated decades ago, as well as to target different populations and settings, including children.

See Figure 2 for an explanation of the structure of our systematic review and relevant factors for the indoor environment.

Figure 2. Description of this Cochrane review. URT = upper respiratory tract.



OBJECTIVES

To evaluate the effectiveness of interventions that increase indoor air humidity to prevent or reduce dryness symptoms of the eyes, the skin and the upper respiratory tract (URT) or URT infections at work and in educational settings.

METHODS

Criteria for considering studies for this review

Types of studies

We will include:

- cluster-randomised controlled trials (RCTs) where the intervention is delivered at the group level, and
- quasi-randomised studies, where the method of randomisation is not truly random, such as alternation.

Because humidification of the air is an intervention that will always take place at a group level and is provided outside the clinical setting, randomisation at the individual level is impossible. Therefore we will also include the following non-randomised study types:

- controlled before-and-after studies, where the outcome is measured in both the intervention and the control group twice, once before and once after the intervention, and
- interrupted time-series studies, where outcomes are measured at least three times before the intervention and three times after the intervention.

Because we expect that the effect on symptoms will be quick and

will also disappear quickly after the intervention has stopped, we will also include randomised and non-randomised cross-over studies.

Types of participants

We will include studies conducted with:

1. Adults (18 years or older) working in any occupational sector and in any professional activity.
2. School age children, adolescents and young adults (up to a maximum age of 30 years) in an educational setting (e.g. kindergarten/pre-school/nursery school, daycare centers, schools, colleges and high schools/universities).

If only a subset of relevant participants is included in a study, we will include this study in the review if minimal data for this group can be extracted, including data about the intervention and the control group. We will make it clear to the reader that the included data are only a subset of the study. We will include both studies that can be considered preventive because participants are free of symptoms at the start of the study and have not requested any intervention, and studies that can be considered remediating because the participants complain of symptoms and have requested measures to improve their symptoms.

Types of interventions

We will include studies evaluating the effectiveness of any intervention aiming to increase indoor air humidity. We will categorise interventions as:

1. central interventions, i.e. at building level, air conditioning with humidification,
2. local interventions, i.e. at room level, use of separate humidifying devices, and
3. other interventions such as putting plants around the workplace, etc.

We will include studies that compare the effectiveness of an air humidifying intervention to a no intervention control group or to an alternative intervention.

Technically, air humidity can be regulated with different types of humidifiers: steam humidifiers produce vapour by thermal evaporation, cold atomisers atomise water with a high-frequency ventilator and the so-called ultrasound atomisers create vapour by ultrasound waves (Fidler 1989).

To be included, a study has to specify absolute (AH) or relative air humidity estimates (RH) of the intervention and the control areas or settings. Alternatively, natural ventilation will be compared as such, e.g. with varying levels of RH.

We will exclude studies that compare the health effects of ultra-dry indoor spaces with uncontrolled indoor spaces, as there is no intervention to increase air humidity.

Types of outcome measures

Primary outcomes

1. Eye symptoms. These can be self-reported eye symptoms such as dry eyes, itching eyes or other physical symptoms of the eye, or objectively measured outcomes such as the blinking rate.
2. Skin symptoms. These can be self-reported skin symptoms such as a dry or itching skin or objectively measured by e.g. a corneometer.
3. Upper respiratory tract (URT) symptoms and health conditions related to the quality of the mucosa, such as rhinitis, rhinosinusitis, the common cold, sore throat, hoarseness, cough, throat inflammation or irritation, laryngitis, tonsillitis and otitis media. We will include both self-reported and physician-diagnosed conditions.

Secondary outcomes

1. Perceived air quality: air dryness, stuffy air, or a general assessment of air quality.
2. Sick leave or absence from work, school or education measured as episodes or duration.
3. Task performance, productivity and attendance.
4. Costs of the intervention to increase indoor air humidity.
5. Adverse effects.

Since effects of indoor air humidity on symptoms and infections may be observed after very short (days) as well as longer time periods (months), we will consider the following time scales:

- up to one month;
- between one month and three months (one season); and
- longer than three months, covering several seasons.

Exclusion criteria

This focus allows us to detect specific seasonal patterns with indoor heating and non-heating periods that also impact and contribute to dryness symptoms of the mucosa. Therefore, we will exclude studies conducted in buildings situated in tropical and subtropical climates to avoid mixed climatic patterns.

If data are reported, we will distinguish between allergic and non-allergic symptoms and illness, and will exclude the former.

Search methods for identification of studies

Electronic searches

We will adapt the MEDLINE search strategy proposed in Appendix 1 to the databases listed below. Sensitivity and precision of the search strategy have to be balanced. Our approach is based on sensitivity in order to be able to identify the relevant

information. Our search includes: a) the intervention and application methods used, b) targeted physiological systems and related symptoms, syndromes, infections and illness, c) effects on occupational or educational attendance, and d) workplace and educational settings in general and specific ones. The study design is not included in our search strategy as there have been different terminologies used during the past decades. We target this aspect within the screening process.

We will include studies published as full text, abstracts as well as unpublished results and we will consider studies in all languages.

We will also conduct a search of unpublished trials in ClinicalTrials.gov (www.Clinical Trials.gov) and the WHO trials portal (www.who.int/ictrp/en/).

We will conduct electronic searches within the following databases:

Health/biomedical

- Ovid MEDLINE with available non-indexed citations (1946 to present)
- EMBASE (1947 to present)
- CENTRAL (Cochrane Library)
- PsycINFO (1806 to present), PsycArticles, Psyndex

Occupational safety and health

- NIOSHTIC-2 (from inception to present)
- HSELINE (from inception to present)
- CISDOC (from inception to present)
- In-house database of the Division of Occupational and Environmental Medicine, University of Zurich (this database results from a manual search in the Current Contents Life Sciences and the main journals of occupational and environmental health. It includes more than 50 journals in occupational and environmental health, internal medicine, epidemiology, nephrology, and toxicology, and covers the period from 1986 to December 2013)

Interdisciplinary

- Web of Science (1988 to present)
- Scopus (1960 to present)

Searching other resources

We will carefully check the reference lists of articles and reviews for any additional eligible studies.

We will search publications from the websites of governmental agencies, such as the Centers for Disease Control - The National Institute for Occupational Safety and Health (NIOSH), the United States (US) Environmental Protection Agency (EPA), American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE), Canadian Centre for Occupational Health and Safety (CCOHS), Partnership for European Research in Occupational Safety and Health (PEROSH), and European Union (EU) guidelines.

We will contact occupational medicine and health specialists for additional references and grey literature. Where necessary, we will seek missing data from authors.

Data collection and analysis

Selection of studies

After removal of duplicate studies, two review authors (KB, DI) will independently screen titles and abstracts for inclusion. If necessary for the decision process, we will read full texts. We will resolve inconsistencies or disagreements through discussion and by consultation with other review authors (MP, MM, HD) where necessary. We will carefully record the process of study selection in order to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009). Data included will cover the study design, the participants, the type and technique of the intervention, the outcome measures and a final assessment for inclusion. We will use Covidence for study screening and data extraction.

Should our systematic searches identify studies conducted by authors of this review, we will avoid conflict of interest by having all decisions concerning inclusion and exclusion made by review authors who were not involved with the study.

Data extraction and management

We will use a data collection form for study characteristics and outcome data shown in Appendix 2 which has been piloted on two studies in the review. Two review authors (KB, DI) will extract study characteristics from included studies. A second author (HD or MM) will review a random selection of data collection forms for accuracy and completeness.

We will extract the following study characteristics:

1. General and context information: study identifier (ID), report ID, citation, year of publication, first author, contact author, affiliation, country, funding information, conflict of interest (declared and if appropriate, suspected (e.g. coworker of a relevant company)), environmental factors: season, urban or rural, type of the building, facility type
2. Methods: aim(s) and objective(s) of the study, study design, total study duration, study location, date of study, sample size considerations and power calculation statistical tests used, withdrawals, dealing with missing data
3. Participants: number of subjects included, selection procedure, participation, representativeness, inclusion criteria, exclusion criteria, study setting, professional activity, mean age or age range (median, percentiles), sex/gender, sociodemographic

characteristics (e.g. smoking status, alcohol intake, socioeconomic level, co-morbidities, medication, atopy, family history)

4. Interventions: types/description/content of intervention and comparison (including type of humidification), time period of intervention and comparison, duration of intervention and comparison, intensity of intervention and comparison, co-interventions, economic information. assessment of air humidity level, control humidity level, recorded outdoor and indoor climatic parameters (e.g. temperature)

5. Outcomes: definition/criteria and description of primary and secondary outcomes specified and collected, and at which time points reported or/and measured, source of outcome criteria, person measuring/reporting, outcome measurement (subjective: self-reported questionnaire (scales), interview (explanation to the participants), objective: physiologic measurements), severity of condition, diagnostic criteria if applicable, validation of outcome tools

6. Results: humidity effects (self-reported, results of scales and/or measured by physiological tests), adjusting for potential confounders

Two review authors (KB, DI) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (HD, MM, MS or MP). One review author (KB or DI) will transfer data into Covidence and then transfer them to the Review Manager (RevMan 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (HD or MM) will spot-check study characteristics for accuracy against the trial report. Should we decide to include studies published in one or more languages in which our author team is not proficient, we will arrange for a native speaker or someone sufficiently qualified in each foreign language to fill in the data extraction form.

Assessment of risk of bias in included studies

Following piloting to calibrate the assessments by KB, DI, HD, MM, MP, MS, two authors (KB, DI, HD or MM) will independently assess the risk of bias of all included studies. We will resolve disagreements through discussion and we will consult another author (MS or MP) where necessary.

We will use the Cochrane standard 'Risk of bias' (RoB) tool to assess risk of bias in controlled studies. We will assess interrupted time-series (ITS) studies with the Effective Practice and Organisation of Care (EPOC) RoB Tool (EPOC 2015).

We will use the following items to assess the risk of bias in randomised controlled studies:

- Sequence generation
- Allocation concealment
- Blinding of participants or organisations if applicable, and outcome assessors
- Incomplete outcome data
- Selective outcome reporting

We have decided to use another additional item: 'control for confounders'.

In the case of self-reported questionnaires, blinding is not applicable for the outcome assessment tool.

For ITS studies, we will base the assessment on the following areas:

- Intervention independent of other changes
- Shape of intervention pre-specified
- Interventions affect outcome data
- Allocation concealment
- Incomplete outcome data
- Selective outcome reporting

Regarding cross-over studies, we will apply suggested questions for assessing risk of bias from the*Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 16.4.3):

- Was use of a cross-over design appropriate?
- Is it clear that the order of receiving treatments was randomised?
- Can it be assumed that the trial was not biased from carry-over effects?
- Are unbiased data available?

For each of these items, we will provide one of the following summary assessments:

- Low risk of bias: plausible bias unlikely to alter the results
- Unclear risk of bias: plausible bias that raises some doubt about the results
- High risk of bias: plausible bias that seriously weakens confidence in the results

To judge risk of bias in randomised controlled studies as well as in ITS, we will use the criteria proposed by EPOC 2015 as well as criteria from the *Cochrane Handbook* (table 8.5.d). With regard to the additional item 'control for confounders', we will first judge if there are important differences between groups prior to the intervention according to confounders. If yes, we will assess whether these relevant confounders were controlled by means of study design (e.g. randomisation, restriction, matching) or in the evaluation of results (e.g. stratification, statistical modelling). We will consider the risk of bias to be low if there are any important differences between groups or if 60% or more of the relevant confounders were controlled in the assessed study. Otherwise we will classify the domain as 'high risk of bias'. We will give a rating of 'unclear risk' if the information is insufficient or lacking. The relevant confounders are season (outdoor air), personal characteristics (e.g. age, gender), comorbidities, atopic conditions and co-exposure in the workplace or in the educational setting.

We will summarise the risk of bias within and across studies for the primary outcomes.

We consider allocation concealment, blinding of participants and outcome assessors and incomplete outcome data to be key domains. We will judge a study to have a high risk of bias when we judge one or more key domains to have a high risk of bias. Conversely, we will judge a study to have a low risk of bias when we judge low risk of bias for all key domains. We will summarise the 'Risk of bias' judgments across different studies for each of the domains listed.

We will summarise and present data in a 'Risk of bias' summary together with a 'Risk of bias' graph as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where information on risk of bias relates to unpublished data or correspondence with the author, we will note this in the 'Risk of bias' table.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse data from studies involving working populations and from studies involving children separately.

We will report the absolute or relative indoor air humidity as continuous variables. We will use the mean difference to assess the intervention effect.

Predominantly, we expect to find outcome data that are dichotomous, such as as percentages of participants affected. Data on symptom severity or absence-related data are probably reported as continuous data. In situations where data for the same outcome are presented in some studies as dichotomous data and in other studies as continuous data, we will calculate continuous measures or, alternatively, we will obtain these data from investigators. As this might not be feasible for older studies, we will present data in three different ways: by entering the means and standard deviations as continuous outcomes, by entering the counts as dichotomous outcomes and by entering all of the data in text form as 'Other data' outcomes.

Furthermore, we will include statistical approaches available which will re-express odds ratios as standardised mean differences (and vice versa), allowing dichotomous and continuous data to be pooled together. We will do this as proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and after consultation with a biostatistician.

We will enter the outcome data for each study into the data tables in RevMan (RevMan 2014) to calculate the intervention effects. We will use risk ratios for dichotomous outcomes, mean differences or standardised mean differences for continuous outcomes, and other types of data as reported by the authors of the studies. If only effect estimates and their 95% confidence intervals or standard errors are reported in studies, we will enter these data into RevMan using the generic inverse variance method. We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader and report where the directions were reversed if this was necessary. When the results cannot be entered in either way, we will describe them in the 'Characteristics of included studies' table, or enter the data into additional tables.

For ITS studies, we will extract data from the original papers and re-analyse them according to the recommended methods for analysis of ITS designs for inclusion in systematic reviews (Ramsay 2003). For ITS studies, we will use the standardised change in level and change in slope as effect measures.

Unit of analysis issues

For studies that employ a cluster-randomised design and that report sufficient data to be included in the meta-analysis but do not make an allowance for the design effect, we will calculate the design effect based on a fairly large assumed intra-cluster correlation of 0.10. We base this assumption of 0.10 being a realistic estimate by analogy on studies about implementation research (Campbell 2001). We will follow the methods stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) for the calculations.

Dealing with missing data

We will contact investigators in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data, such as standard deviations or correlation coefficients.are missing, and they cannot be obtained from the authors, we will calculate them from other available statistics such as P values, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We will assess the clinical homogeneity of the results of included studies based on similarity of population, intervention, outcome and follow-up.

We will consider populations as similar when they belong to the same subgroup (working adults or children/young adults in education).

We will consider interventions as similar when they include indoor air humidification with:

1. an air conditioning system (centrally located system), or
2. local, office-based humidifiers, or

3. other measures to increase indoor air humidity, such as for instance putting plants around the workplace, or placing a container of water or wet clothes in proximity to a radiator or a heating system.

We will consider outcome measurements as similar enough to combine when:

1. subjective symptoms are assessed (stratified by symptom group: eye, skin, URT, combined) and when
2. objective measurements are performed (stratified by targeted organ: eye, skin, URT, combined).

We will regard outcomes measured within the following categories of follow-up times to be similar enough to combine:

1. up to one month,
2. between one month and three months (one season), and
3. more than three months (several seasons).

According to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) we will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by pre-specified subgroup analysis.

Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

(For interpreting I^2, Higgins 2011 suggests:

- I^2 = 0%; no heterogeneity,
- I^2 = 25%; low heterogeneity,
- I^2= 50%; moderate heterogeneity,
- I^2 = 75%; high heterogeneity.)

*The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2).

In addition, we will report the 95% confidence interval of I^2 to present the uncertainty in I^2.

Assessment of reporting biases

If we are able to pool more than five trials in any single meta-analysis, we will create and examine a funnel plot to explore possible small study biases.

Data synthesis

When it comes to deciding how to construct comparisons and what results to pool, we will follow the advice given by Verbeek 2012. We will analyse studies with different designs separately. We plan to combine studies that we consider similar regarding participants, intervention, control and study duration. We will pool the results and analyse them statistically if appropriate.

We will pool data from studies judged to be clinically homogeneous using Review Manager 5.3 software (RevMan 2014). If more than one study provide usable data in any single comparison, we will perform meta-analysis. We will use a random-effects model when I^2 is above 40%; otherwise we will use a fixed-effect model. When I^2 is higher than 75% we will not pool results of studies in meta-analysis.

For ITS, we will perform separate meta-analyses for level and slope using the generic inverse variance method.

We will narratively describe skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. RH of 30% versus natural ventilation and RH of 50% versus natural ventilation) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

As the evidence might be too heterogeneous for statistical pooling purposes, we will consider conducting a harvest plot, a form of evidence synthesis that has been shown to be an effective way to synthesise evidence for complex interventions (Ogilvie 2008; Turley 2013). Harvest plots help to synthesise evidence graphically based on all study designs for the differential effects of humidification across all primary and secondary outcomes.

'Summary of findings' table

We will create 'Summary of findings' tables using the outcomes of eye, skin and upper respiratory tract (URT) symptoms and health condition, measured as self- or physician-reported symptoms or condition or as any type of specific physiological measurement. We will use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary.

We will analyse and report results regarding prevention or reduction (of symptoms or infections) separately.

We will present the data separately for the two subgroups, working adults and children/young adults in education.

We will grade the evidence yielded by each comparison as one of the following:

- High quality - further research is very unlikely to change our confidence in the estimate of effect;
- Moderate quality - further research is likely to have an

important impact on our confidence in the estimate of effect and may change the estimate;

- Low quality - further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low quality - any estimate of effect is uncertain.

We will also compile an additional GRADE table showing all our decisions about the quality of evidence and their justifications.

Subgroup analysis and investigation of heterogeneity

If we have enough included studies, we plan to undertake subgroup analyses by professional activity (office workers compared to non-office workers e.g. healthcare workers in hospitals), and by gender. We will compare studies where over 50% of participants are office workers with studies where less than 50% are office workers. Similarly we will compare studies where over 50% or participants are female with studies where less than 50% of participants are female. We will use the following outcomes in subgroup analyses:

1. Any effect (prevention or reduction of symptoms or symptom score) on dryness symptoms of the mucosa (eye or URT) or the skin;
2. Any effect (prevention or reduction of symptoms) on URT infections or illness (e.g. rhinitis, rhinosinusitis, common cold, sore throat, throat inflammation, laryngitis, tonsillitis, otitis media);
3. New onset of adverse events.

We will use the Chi² test to test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

If there are sufficient included studies, we will perform sensitivity analysis defined a priori to assess the robustness of our conclusions. This will involve:

- including only studies judged to have a low risk of bias, and
- including only studies that use objective outcome measurements.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice based on more than just the evidence, such as values and available resources. Our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present.

#	Searches
1	Humidity/
2	humid*.ti,ab.
3	(indoor* or inside or building* or room* or plant*).ti,ab.
4	(1 or 2) and 3
5	air conditioning/ or ventilation/

(*Continued*)

6	(air adj3 (condition* or cooling or ventilation or sparging)).ti,ab
7	ventilation.ti,ab.
8	4 or 5 or 6 or (7 and 3)
9	((indoor and (air or environmental)) adj3 quality).mp.
10	(iaq or ieq).ti,ab.
11	or/8-10
12	Eye Diseases/ or Skin Diseases/ or Nose Diseases/ or Nasal Obstruction/ or rhinitis/ or rhinitis, atrophic/ or rhinitis, vasomotor/ or Respiration Disorders/ or Sinusitis/ or Cough/ or Hoarseness/ or Common Cold/ or Laryngitis/ or Pharyngitis/ or Tonsillitis/ or Otitis Media/ or Keratoconjunctivitis Sicca/ or Dry Eye Syndromes/
13	(dryness or irritation* or rhinitis or rhinosinusitis or Cough or Hoarseness or "common cold" or Laryngitis or Pharyngitis or Tonsillit* or "Otitis Media" or "Keratoconjunctivitis sicca" or sneezing).ti,ab
14	Sick Building Syndrome/ or sick building syndrome.ti,ab.
15	((nose or nasal) adj3 (disease* or symptom* or runny or running or stuffed or dry* or obstruction)).ti,ab
16	(throat adj3 (disease* or symptom* or sore or irritat* or inflam*)).ti,ab
17	(eye* adj3 (disease* or symptom* or red* or dry* or burning or irritat*)).ti,ab
18	(skin adj3 (disease* or symptom* or condition* or red* or irritat* or itch* or dry* or rash)).ti,ab
19	((sinus or respiratory) adj3 (disease* or symptom* or condition* or health)).ti,ab
20	Absenteeism/ or Sick Leave/
21	((sick or illness or disability) adj3 (leave* or day*)).ti,ab
22	((absenteeism or attendance or attainment or productivity or performance) adj9 (job or work or office or school or preschool* or "pre-school*" or kindergar#en* or daycare or "day care")).ti,ab
23	("mucous membrane" or mucosa or mucosal).ti,ab.
24	mucous membrane/ or exp respiratory mucosa/
25	or/12-24
26	Workplace/ or exp Schools/ or Child Day Care Centers/ or Occupational Exposure/ or Environment, Controlled/ or (office or Work* or job or laboratory or school* or preschool* or "pre-school*" or kindergar#en* or daycare or "day care" or classroom* or education or occupation*).ti,ab

(*Continued*)

27	11 and 25 and 26

Appendix 2. Study screening form

I. General information

Study screening and data extraction will be performed in Covidence.

Study ID:	Report ID:	Data form completed: Version number:
First author:	Year of study:	Data extractor:
Citation:		
Publication type (specify):		
Country of study:	Funding source of study:	Potential conflict of interest from funding? Yes - No - Unclear

II. Study eligibility

Type of study	Randomised controlled trial (RCT) Cluster randomised controlled trial (cluster-RCT) Interrupted time-series studies (ITS) - clearly defined intervention point Cross-over study - order of intervention	Controlled before-and-after study (CBA) - comparable control site Quasi-randomised studies - method of allocation Other type of controlled studies, specify:
	Does the study design meet the criteria for inclusion? Yes No: exclude Unclear	
Type of participants	Describe the participants included: They belong to which group: - Adult working population - School setting: children, young adults Do the participants meet the criteria for inclusion? Yes No: exclude Unclear	
Type of interventions	Is indoor air humidity assessed? Technique: Intervention in control group:	

(*Continued*)

	Does the intervention meet the criteria for inclusion? Yes No: exclude Unclear
Type of outcome measures	List primary outcomes: List secondary outcomes: Does the study assess a single primary or secondary outcome, qualifying it for inclusion? Yes No: exclude Unclear

III. Summary of assessment for inclusion

Include in review	Exclude from review
Reason for exclusion:	
Independently assessed and then compared? Yes No	Differences resolved? Yes No
Request further details? Yes No Contact detail of authors:	
Notes:	

Do not proceed if article is excluded from review.

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: AF, CH, HD, MM, MP, MS

Designing the protocol: AF, HD, MM, MP, MS

Coordinating the protocol: MM

Designing search strategies: M. Gosteli (specialised librarian), MM

Writing the protocol: KB, DN, MM

Providing feedback on the protocol drafts: all authors

Providing general advice on the protocol: DN, HD, MP

DECLARATIONS OF INTEREST

Katarzyna Byber: None known.

Aline Flatz: None known.

Dan Norbäck: None known.

Christine Hitzke: None known.

David Imo: None known.

Matthias Schwenkglenks: None known.

Milo Puhan: None known.

Holger Dressel: None known.

Margot Mutsch: None known.

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Internal sources

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External sources

- Cochrane Switzerland and Swiss School of Public Health (SSPH+), Switzerland.

Salary to Aline Flatz

- Clinic of Occupational and Environmental Medicine Department, University Hospital, Uppsala, Sweden, Sweden.

Infrastructure and salary to Dan Norbäck

NOTES

Parts of the methods section and Appendix 1 of this protocol are based on a standard template established by the Cochrane Work Group.